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Chetan, M R; Charlton, M H; Thompson, C; Dias, R P; Andrews, R C; Narendran, P

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DR MADHURIMA CHETAN (Orcid ID : 0000-0002-6868-4969)

DR PARTH NARENDRAN (Orcid ID : 0000-0002-4583-8793)

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Corresponding author mail id: madhurima.chetan@doctors.net.uk

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## **The Type 1 diabetes ‘honeymoon’ period is five times longer in men who exercise: a case–control study**

Type 1 diabetes mellitus is an autoimmune disorder characterized by the destruction of insulin-secreting  $\beta$  cells, and subsequent insulin deficiency. Shortly after diagnosis, 60% of adults with Type 1 diabetes experience a period of partial remission, or ‘honeymoon’ period, characterized by low insulin requirement and good glycaemic control [1].

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Historically, the honeymoon period was defined as an insulin requirement of  $\leq 0.5$  units/kg/day together with  $\text{HbA}_{1c} \leq 58$  mmol/mol (7.5%). Currently, the honeymoon period is defined as insulin dose-adjusted  $\text{A}_{1c}$  ( $\text{IDAA}_{1c}$ )  $\leq 9$ , where  $\text{IDAA}_{1c} = \text{HbA}_{1c} (\%) + [4 \times \text{insulin dose (units/kg/day)}]$  [2]. This shows good correlation with stimulated C-peptide, and therefore endogenous insulin secretion [2].

The honeymoon period is attributed to two factors: partial recovery of  $\beta$ -cell function and normalization of insulin sensitivity. Both decline with duration of Type 1 diabetes, bringing the honeymoon period to a natural close.

We hypothesized that physical exercise is associated with a longer honeymoon period in newly diagnosed Type 1 diabetes.

For this retrospective study, we identified 16 men who self-reported undertaking significant physical exercise, both at the time of Type 1 diabetes diagnosis and throughout their Type 1 diabetes follow-up, from three UK diabetes clinics (adult clinic in a teaching hospital, adult clinic in a district general hospital, and paediatric clinic in a teaching hospital). For each case, two controls, matched for age, sex and BMI at time of diagnosis, who self-reported low levels of physical activity, were selected from the same clinic population.

Data were collected retrospectively on type and duration of exercise, daily insulin requirement,  $\text{HbA}_{1c}$  and weight using clinic letters. Bolus insulin doses were not available for most people; daily insulin requirement was calculated as twice the basal insulin dose. Honeymoon period duration was defined as the last clinic visit when  $\text{IDAA}_{1c} \leq 9$ .

Non-parametric unmatched analyses were used. The Kruskal–Wallis test was used to compare age, BMI and follow-up duration. The chi-square test was used to compare presentation and antibody status. Kaplan–Meier analysis and log-rank test were used to compare the duration of the honeymoon period. Statistical analyses were performed using IBM SPSS Statistics version 25.0 for Macintosh. Figures were generated using GraphPad Prism version 7.00 for Macintosh.

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Age, BMI, follow-up duration and antibody status were similar in both groups. There was significantly more ketoacidosis at first presentation in controls than cases (Table S1). The estimated median honeymoon period was 33.0 months [95% confidence intervals (CI) 24.9–41.1] in cases, compared with 6.0 months (95% CI 2.3–9.7) in controls (log-rank  $P < 0.0001$ ). This significant difference was maintained in an antibody-positive subgroup and a non-ketoacidosis subgroup.

Our results show that the Type 1 diabetes honeymoon period is more than five times longer in men undertaking high levels of physical exercise, compared with age-, sex- and BMI-matched sedentary controls (Fig. 1).

This study has limitations: small sample size, no formal measurement of physical activity, estimation of bolus insulin dose and reduced sensitivity of IDAA<sub>1c</sub> in adults. For some men, the diagnosis of Type 1 diabetes was purely clinical and not supported by antibody testing. The study group was male and mostly adult. Future studies need to characterize the honeymoon period in physically active women and children with Type 1 diabetes.

A strength of this study is the use of IDAA<sub>1c</sub> to define the honeymoon period; this is validated to correlate with endogenous insulin secretion [2]. A further strength is matching for age, sex and BMI, and adjusting for antibody status and ketoacidosis using subgroup analysis. These factors all associate with rate of  $\beta$ -cell loss. Other unmeasured factors may affect the honeymoon period, e.g. smoking, diet and insulin regime. Being an association study, causality cannot be assumed.

We propose that exercise prolongs the honeymoon period through an increase in both insulin sensitivity and  $\beta$ -cell function. Improved insulin sensitivity with exercise has been demonstrated in various Type 1 diabetes populations [3]. There is good evidence that exercise improves  $\beta$ -cell function in Type 2 diabetes mellitus and in animal models of Type 1 diabetes [4]. Furthermore, recent work we have undertaken suggests that exercise improves  $\beta$ -cell function in Type 1 diabetes when the outcome measure is corrected for the improved insulin sensitivity that occurs with exercise [5].

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The honeymoon period, and its contributory factors, have important clinical benefits. Endogenous insulin secretion is associated with improved HbA<sub>1c</sub>, less hypoglycaemia and reduced rates of microvascular complications [6]. Improved insulin sensitivity is associated with fewer vascular complications [7]. The occurrence of a honeymoon period per se is associated with fewer microvascular complications [8].

This is the first study to examine the effect of physical exercise on the honeymoon period. Our data suggest an important role for exercise in new-onset Type 1 diabetes. There is now a need for a formal randomized controlled trial to investigate whether exercise prolongs the honeymoon period and to explore the underlying mechanisms.

#### **Funding sources**

#### **Competing interests**

**M. R. Chetan<sup>1</sup>, M. H. Charlton<sup>2</sup>, C. Thompson<sup>3</sup>, R. P. Dias<sup>1,4</sup>, R. C. Andrews<sup>3,5</sup> and P. Narendran<sup>1,2</sup>**

*<sup>1</sup>College of Medical and Dental Sciences, University of Birmingham and <sup>2</sup>Department of Diabetes, University Hospitals Birmingham NHS Foundation Trust, Birmingham, <sup>3</sup>Department of Diabetes, Taunton and Somerset NHS Foundation Trust, Taunton, <sup>4</sup>Department of Paediatric Endocrinology and Diabetes, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, and <sup>5</sup>University of Exeter Medical School, University of Exeter, Exeter, UK*

## References

- 1 Schölin A, Berne C, Schvarcz E, Karlsson FA, Björk E. Factors predicting clinical remission in adult patients with type 1 diabetes. *J Intern Med* 1999; **245**: 155–162.
- 2 Mortenson, Henrik B., Hougaard, Philip, Swift P. New definition for the partial remission period in children and adolescents with type 1 diabetes. *Diabetes Care* 2009; **32**: 1384–1390.
- 3 Chimen M, Kennedy A, Nirantharakumar K, Pang TT, Andrews R, Narendran P. What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. *Diabetologia* 2012; **55**: 542–551.
- 4 Narendran P, Solomon TP, Kennedy A, Chimen M, Andrews RC. The time has come to test the beta cell preserving effects of exercise in patients with new onset type 1 diabetes. *Diabetologia* 2015; **58**: 10–18.
- 5 Narendran P, Jackson N, Daley A, Thompson D, Stokes K, Greenfield S *et al.* Exercise to preserve  $\beta$ -cell function in recent-onset Type 1 diabetes mellitus (EXTOD) – a randomized controlled pilot trial. *Diabet Med* 2017; **34**: 1521–1531.
- 6 Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care* 2003; **26**: 832–836.
- 7 Orchard TJ, Olson JC, Erbey JR, Williams K, Forrest KY-Z, Smithline Kinder L *et al.* Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes: 10-year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care* 2003; **26**: 1374–1379.

- 8 Niedzwiecki P, Pilacinski S, Uruska A, Adamska A, Naskret D, Zozulinska-Ziolkiewicz D.  
Influence of remission and its duration on development of early microvascular complications  
in young adults with type 1 diabetes. *J Diabetes Complicat* 2015; **29**: 1105–1111.

**FIGURE 1.** Honeymoon period in 16 physically active cases and two age-, sex- and BMI-matched sedentary controls per case.

### <H1>Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Kaplan–Meier plot of the Type 1 diabetes honeymoon period in physically active cases and matched sedentary controls.

**Table S1.** Baseline characteristics of 16 physically active cases and two age-, sex- and BMI-matched sedentary controls per case.

**Table S2.** Type and frequency of exercise undertaken by 16 physically active men with Type 1 diabetes.

